REMARKS

Formal Matters

Claims 23-28, 30-31 and 33-38 are pending.

Claims 23-28, 30-31 and 35 were examined and rejected.

Claim 23 is amended. The amendment was made solely in the interest of expediting prosecution, and is not to be construed as an acquiescence to any objection or rejection. Support for the amendment is found in page 9, lines 13-15. Accordingly, no new matter is added.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claims 23-28, 30-31 and 35 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Without wishing to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 23 has been amended to recite an *antagonist* anti-CCR4 antibody. Since the Office has indicated that the specification is enabling for a method of inhibiting trafficking of systemic memory T cells to a site of inflammation by administering an antagonist anti-CCR4 antibody (see first paragraph of this rejection in the Office Action), this rejection is believed to have been addressed.

In view of the foregoing discussion, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103 – Wells in view of Heath

Claims 23-28, 30 and 35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wells (U.S.P.N. 6,150,132) in view of Heath (J. Clin. Invest. 1997 99:178-184). Specifically, the Office Action asserts that Wells' suggestion to use a CCR4 antagonist to release histamine from basophils, in combination with Heath's suggestion to use antibodies as chemokine receptor antagonists, renders the subject matters of the instant claims obvious. The Applicants respectfully traverse this rejection.

The Office acknowledges that this rejection is based on a theory of inherency. The Office reasons that Wells' method of blocking release of histamines from basophils using Heath's antibody approach would provide a method that *inherently* inhibits trafficking of systemic memory T cells. The Applicants respectfully submit that this is not the case.

Factual support for the Applicants position is set forth below.

This rejection is based on a theory of inherency. The MPEP at § 2112 provides very clear guidance for establishing rejections based on inherency: "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic."[1] (emphasis in the original). Accordingly, in order for such a rejection to be correctly established, according to the MPEP, a claim limitation that is not explicitly taught must be inherent, i.e., necessarily present, in the cited prior art. The mere possibility that the limitation is taught in the art is not sufficient to merit such a rejection, and the mere fact that a certain thing *may* result from a given set of circumstances is also not sufficient.[2]

The Applicants respectfully submit that a method of blocking release of histamines from basophils does not inherently inhibit trafficking of systemic memory T cells because histamine release from basophils can occur in the absence of systemic memory T cells trafficking. Histamine is not a modulator of systemic memory T cell trafficking, and memory T-cell trafficking is not an event that necessarily occurs after histamine release from basophils. Accordingly, a method of blocking release of histamines from basophils does not necessarily inhibit trafficking of systemic memory T cells. As such, while the Office may argue that there is a *possibility* that Wells basophil methods (see Wells col. 2, lines 1-2) *may* inhibit trafficking of memory T cells, the fact that such a possibility exists is insufficient grounds, according to the MPEP and current law, to reject the instant claims. In other words, a method of inhibiting memory T cell trafficking is not an inherent property of a method of blocking histamine release from basophils, and, as such, this rejection should be withdrawn.

Further, the Applicants respectfully submit that if the Office consistently took a similar position to that set forth in this rejection, no claims directed to new methods of using known compositions would

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[1] MPEP at § 2112, citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)

[2] MPEP at § 2112 "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

ever be patentable. For example, if the Office takes the position that has taken in this case, a method of using a known compound to treat Alzheimer's disease would be unpatentable over a method of using the same compound to treat inflammation. New ways of using known compositions are quite patentable, according to the MPEP and current law[3]. Accordingly, the Applicants respectfully submit that this rejection is unfounded, and not based on current law.

The Office cites *Ex parte Novitski* in support of this rejection. However, the fact pattern of *Novitski* is distinguished from that of the instant case because *Novitski* is concerned with administering a known compound (in this case a certain bacterium) to a population of Wisconsin 526 plants in which susceptible nemotode and fungi were necessarily present together (and acknowledged as being present in the disputed patents). The instant claims are concerned with methods of using a previously unknown compound (i.e., an inhibitory anti-CCR4 antibody) for a method (i.e., inhibiting memory T cell trafficking) that is not necessarily inherent to a method assertedly suggested in the prior art (histamine release). Accordingly, the findings of *Ex parte Novitski* are inapposite to the instant claims.

Further, as discussed above, this rejection is based on the Office's argument that one of skill in the art would combine Wells and Heath to provide a method of inhibiting histamine release. The Office argues that such a method would inherently block memory T cell trafficking. Accordingly, if the Applicants can show that Wells and Heath cannot properly be combined to provide a method of inhibiting histamine release, this rejection falls flat. As will be demonstrated below, one of skill in the art would not combine Wells and Heath with any reasonable expectation of success, and, accordingly, this rejection may be withdrawn.

The Applicants note that at the time of filing, one of skill in the art would not have combined Wells and Heath to provide a method of inhibiting histamine release from basophils because Wells suggestion to modulate histamine release from basophils using a CCR4 antagonist was taught away from at the time of filing of the instant application. In other words, at the time of filing, it was well known that CCR3 and not CCR4 is the receptor that mediates histamine release from basophils, and, accordingly, Wells ahd Heath could not be combined to produce a method of inhibiting histamine release using a CCR4 antagonist with any reasonable expectation of success. Accordingly, Wells and Heath could not

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3 MPEP § 2112.02 "The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957)".

have been combined to inherently provide the present method of inhibiting systemic memory T cell trafficking. Factual support for this argument is set forth below.

Wells' disclosure concludes that MCP-1, MIP-1a and RANTES are ligands for CCR4. Since MCP-1, MIP-1a and RANTES were well known to inducers of histamine release from basophils (see e.g., Kuna et al, J Immunol. 1992 149:636-42, as cited in the IDS filed herewith), Wells postulated that antagonists of CCR4 may be used to reduce histamine release from basophils. However, Wells' conclusions were later refuted by Imai et al. (J. Biol. Chem. 1997 272:15036-15042, as cited in the IDS filed herewith), and others. CCR4 is, in fact, a receptor for TARC and MDC, not MCP-1, MIP-1a and RANTES. Quoting from the end of the last full paragraph of p15039 of Imai: "TARC but not MIP-1a or RANTES is a functional ligand for CCR4". This distinction is described in the background section of the instant application, on lines 9-13 of page 2 therein, and it is currently well understood by the scientific community that MCP-1, MIP-1a and RANTES are *not* ligands for CCR4 (see, e.g., Heinemann, 2000, as cited in the IDS filed herewith) . In fact, and in contrast to Wells' teachings, at the time of filing it was well known that **CCR3** (not CCR4) was the receptor that triggers histamine release from basophils (see, e.g., Uguccioni et al, 1997, as cited in the IDS filed herewith). CCR3 is *not* the subject of the instant claims. Heath, as cited in this rejection, is focused on the role of CCR3 (not CCR4) in eosinophil responses and, as such, fails to support any kind of a role for CCR4 in histamine release from basophils.

TARC and MDC (the true ligands for CCR4) have no effect on histamine release from basophils, and, accordingly, one of skill in the art, at the time of filing, would not practice Wells' method of inhibiting histamine release from basophils using a CCR4 antagonist with any expectation of success. After Wells' publication, the art teaches directly away from CCR4 having anything to do with histamine release. In view of the papers of Imai and Uguccioni, why would one of skill in the art at the time of filing the present application believe that CCR4 was involved in histamine release?

In view of the foregoing discussion, the Applicants respectfully submit that Wells and Heath could not even be combined to provide a method of using an antibody to CCR4 to inhibit histamine release from basophils because such a method would not have been practiced with any reasonable expectation of success at the time of filing. In other words, the Applicants respectfully submit that one of skill in the art would not have combined, with any reasonable expectation of success, Wells and Heath, in view of the teachings of Imai and Uguccioni, to produce a method of using an antibody to

CCR4 to inhibit histamine release from basophils. Since the combination of Wells and Heath provides no explicit suggestion of a method for inhibiting systemic memory T-cell trafficking, the Applicants respectfully submit that the Office's position lacks weight, and this rejection should be withdrawn.

Finally, and solely to preserve the arguments for Appeal, the Applicants respectfully restate their previous arguments below.

With regard to obviousness, the M.P.E.P. teaches at §1242 that:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Thus, in order for a proper *prima facie* case to be established with a combination of references, all the elements of the claimed invention must be suggested in the references, and the invention must be suggested with a reasonable expectation of success.

The Applicants respectfully submit that Wells and Heath fail to teach an element of the rejected claims, namely a *systemic memory T-cell*. Furthermore, neither Wells nor Heath provide any indication that CCR4 (in view of the multitude of other chemokine receptors) would be a chemokine receptor useful in the claimed methods, and, as such, a skilled person would have no reasonable expectation of success in combining Wells and Heath to provide the claimed invention. Finally, Heath's negative statements regarding the function of CCR4 teach away from the claimed invention. The Applicants reasoning is set forth below.

The rejected claims are directed to methods involving, *inter alia*, inhibiting trafficking of systemic memory T cells using an anti-CCR4 antibody.

Wells provides the sequence of CCR4, but fails to teach or in any way suggest methods of inhibiting trafficking systemic memory T cells using anti-CCR4 antibodies.

Heath, on the other hand, provides a method in which *eosinophil* chemotaxis is modulated using an anti-*CCR3* antibody, and, according to the Office Action, generally suggests that chemokine receptor antagonists are effective inhibitors of leukocyte recruitment.

Firstly, neither Wells nor Heath mention systemic memory T-cells at any point. Accordingly, Wells and Heath, separately or in combination, fail to teach an element of the claimed invention, i.e., systemic memory T-cells.

On the basis of the foregoing, this rejection may be withdrawn without any further discussion.

Should the Examiner try to assert that the combination of Wells and Heath in some way does teach a method involving systemic memory T-cells, the Applicants respectfully submit that Wells and Heath cannot be combined to provide the claimed invention with any reasonable expectation of success. In other words, the Applicants respectfully submit that Heath's reported success in altering chemotaxis in eosinophils using an anti-CCR3 antibody would not automatically predict success of a method of altering chemotaxis of systemic memory T-cells using an anti-CCR4 antibody.

Heath teaches methods of altering chemotaxis of eosinophils. Eosinophils are not systemic memory T-cells (or even T-cells for that matter), and the Office has presented no reason why a method that works for eosinophils would work with a reasonable expectation of success in systemic memory T-cells. In fact, in view of comments made by Heath (see Heath's entire disclosure, and in particular the first sentence of the third paragraph of the introduction: "Because of the complicated pattern of receptor binding and signaling by the chemokines, it has been difficult to determine the significance of a particular receptor on a given leukocyte type") a skilled person would have no idea which receptor to block in order to effect chemotaxis of systemic memory T-cells. In other words, in view of the teachings of Wells and Heath (in particular the comments made by Heath) a skilled person would not know beforehand which chemokine receptor (e.g., CXCR1, CXCR2, CCR1, CCR2, CCR3, CCR4, or CCR5, or any other chemokine receptor not specifically listed by Wells or Heath) would be a successful target for altering chemotaxis of systemic memory T-cells. In actual fact, prior to filing of this patent application, it was not even known that systemic memory T-cells actually expressed CCR4. Why would a skilled person think that CCR4 is the chemokine receptor responsible for chemotaxis of systemic memory T-cells? The Applicants respectfully submit that the answer to this question is not set forth in

Wells or Heath, or in the Office Action, and it was not until the Applicants made this discovery that the answer became known.

Furthermore, at several positions Heath indicates that CCR4 has no role in chemotaxis of eosinophils. For example:

On page 181 in the first paragraph of the discussion, Heath states the following:

"These results establish that CCR3 is indeed the principal receptor for eosinophil responses to CC chemokines, and ***questions the essential role for*** CCR1, CCR2, ***CCR4*** or CCR5."
(emphasis added)

On page 181 in the second paragraph of the discussion, Heath states the following:

"...our results show that ***a MIP-1α receptor*** [Wells asserts that CCR4 is the receptor for MIP1α and RANTES. See, e.g., Wells column 1, title, and the last paragraph of column 1]. ***contributes little to the functional responses of eosinophils*** to the major eosinophilic chemoattractants: RANTES, MCP-3 or MCP-4".
(emphasis and bracketed material added)

And on page 181 in the second paragraph of the discussion, Heath also states the following:

"...if other CC chemokine receptors are present [e.g., CC chemokine receptors other than CCR3, e.g., CCR4], ***they have a minor functional significance***"
(emphasis and bracketed material added)

In other words, Heath teaches that CCR4 has no role in eosinophil chemotaxis. The Applicants respectfully submit that Heath's comments on the function of CCR4 would, in fact, lead a skilled person *away* from any conclusion that CCR4 is the chemokine receptor responsible for chemotaxis of systemic memory T-cells. Set forth another way, Heath states that CCR4 is functionally insignificant in relation to CCR3 in eosinophils. Since there would be no reason for this not to true in systemic memory T-cells, a skilled person would be more likely to think that CCR3, not CCR4, is the chemotaxis receptor in systemic memory T-cells. This conclusion is supported by fact that Heath found CCR3 in some T-cell

clones (see the second sentence of the second paragraph of Heath's discussion). In view of Heath's teachings, therefore, a skilled person would more likely suspect CCR3, not CCR4 as being the primary receptor for systemic memory T-cells.

This conclusion of a role for CCR3 instead of CCR4 in systemic memory T cells is further bolstered by Uguccioni et al (Exhibit D). Uguccioni found that CCR3, not CCR4, is an important receptor to mediate histamine release from basophils. So at the time of filing, the available art noted the importance of CCR3, and not CCR4 in eosinophils as well as basophils.

Accordingly, even if the combination of Wells and Heath did teach systemic memory T-cells, the subject matter of the rejected claims could not be practiced with any reasonable expectation of success because there is no suggestion that CCR4 is the dominant receptor for systemic memory T-cells. To the contrary, Heath and Uguccioni teach that CCR3, and not CCR4, is the dominant receptor for systemic memory T-cells. Since the subject matter of the rejected claims cannot be practiced with any reasonable expectation of success, this rejection may be withdrawn.

Rejection under 35 U.S.C. §103 – Wells in view of Heath and Bendig

Claim 31 is rejected under 35 U.S.C. §103(a) as being unpatentable over Wells in view of Heath and Bendig (Methods: A Companion to Meth. Enzymol. 1995 8:83-93). Specifically, the Office Action asserts that the methods of identifying a CCR4 antagonist of Wells, in combination with Heath's suggestion to use monoclonal antibodies as chemokine receptor antagonists and Bendig's humanized monoclonal antibodies, renders the subject matters of the instant claims obvious. The Applicants respectfully traverse this rejection.

As established above, Wells and Heath are deficient in that they fail to suggest the claimed method.

Bendig's humanized monoclonal antibodies fail to meet Wells and Heath's deficiencies, and, as such, an element of claim 31, i.e., systemic memory T-cells, is not taught in this rejection.

In view of the foregoing, this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-110CON.

Respectfully submitted,
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Date: July 29, 2004

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